Role of Sp1 expression in gastric cancer: A meta-analysis and bioinformatics analysis

SHUAI SHI and ZHI-GANG ZHANG

Department of Pathology, Cangzhou People's Hospital, Cangzhou, Hebei 061000, P.R China

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Abstract. Sp1 (specificity protein 1) is an important transcription factor that regulates multiple cancer-related genes. A number of published studies have explored the relationship between Sp1 expression and prognosis in gastric cancer. Therefore, a deeper level of understanding is required into the molecular biological mechanism of gastric cancer. Finding new tumor biomarkers for the accurate prediction of occurrence, recurrence and metastasis of gastric cancer are of great significance. The present study uses a systematic meta-analysis and bioinformatics analysis to acquire evidence for a prognosis marker based on Sp1 expression in gastric cancer. A literature search was performed using PubMed and China National Knowledge Infrastructure on 8th June, 2018. A total of 13 studies were included in the meta-analysis. The meta-analysis showed that the expression of Sp1 was significantly higher in gastric cancer tissue, compared with that of normal mucosa [odds ratio (OR), -0.53; 95% CI, -0.62-0.44; P<0.0001] and dysplasia (OR, 0.24; 95% CI, 0.13-0.44; P<0.0001). A positive association was found Sp1 expression and depth of invasion (OR, 0.31; 95% CI, 0.11-0.86), lymph node metastasis (OR, 0.36; 95% CI, 0.22-0.59), TNM staging of gastric cancer (OR, 0.43; 95% CI, 0.24-0.79) and Lauren's classification (OR, 0.83; 95% CI, 0.51-1.36), but not with sex or tumor differentiation (OR, 1.34; 95% CI, 0.95-1.88). According to the Oncomine database, Sp1 mRNA expression is significantly higher in gastric cancer tissues compared with that in normal tissues (P<0.05), including that of intestinal, diffuse and mixed-type gastric carcinomas (P<0.05). Kaplan-Meier plots show that the expression of Sp1 mRNA is negatively associated with overall and progression-free survival rates of patients with gastric cancer, even when stratified according to expression level (P<0.05). The selected prediction parameter is overall survival or progressive-free survival rate. The expression level of Sp1 was divided into high expression group and low expression group according to the best cut off value provided on the Kaplan-Meier plotter. However, Sp1 protein expression is upregulated in gastric cancer tissues compared with normal tissues and is positively associated with depth of invasion and TNM stage of gastric cancer. The high protein expression of Sp1 might make it a good potential marker for the prognosis of patients with gastric cancer.

Correspondence to: Professor Zhi-Gang Zhang, Department of Pathology, Cangzhou People's Hospital, 7 Qingchi Avenue, Cangzhou, Hebei 061000, P.R. China
E-mail: zhzhg001518@126.com

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Introduction

Specificity protein 1 (Sp1) was identified and cloned by Kadonaga *et al* (1) in 1987, and was one of the earliest transcription factors to be identified. Sp1 belongs to the Sp1/Krüppel-like factor transcription factor family of sequence-specific DNA binding proteins (2). Sp1 consists of four activated functional areas (A, B, C and D). The functional domains A and B are rich in glutumamide. Domain C is a highly-charged amino acid enriched area with three zinc fingers at the end of the hydroxyl group. At the same time, the formation of Sp1 tetramers can attract more polymers that bind to DNA, and produces positive feedback regulation of the transcription process (3). Sp1 performs an important regulatory role for a variety of housekeeping genes, including nucleic acid metabolism related genes and oxidative phosphorylation related genes, including mitogen-activated protein kinase 8 and EPH receptor B2 (4,5). Meanwhile, if the promoter of a gene lacks the expression of the TATA box, Sp1 can prevent DNA methylation and maintain gene transcription at the activation state (3).

It has been proven that Sp1 can upregulate the expression of Bcl-2 (6), survivin (7), and TGF-β (8). Studies have shown that Sp1 can form a compound with the Smad protein to induce the transcription of and overexpression of Smad7, and negatively regulates the TGF-β pathway, thus affecting cell growth, differentiation and apoptosis (9). The abnormal activation of Sp1 can also upregulate the expression of tumor-related factors and angiogenic factors that provide a good microenvironment for tumor growth, and promote tumor proliferation, metastasis and angiogenesis in gastric and pancreatic (10). Sp1 is recruited by the promoter of vascular endothelial growth factor for its upregulated expression, promoting vascular endothelial proliferation, angiogenesis and increasing vascular

permeability for tumor growth and metastasis (11). Increased Sp1 expression has been found to be positively associated with a worse prognosis for patients with gastric carcinoma (12).

Reportedly, the expression of Sp1 is significantly increased in esophageal carcinoma, colorectal cancer, pancreatic cancer and thyroid cancer (13-16). Hosoi *et al* (17) found that the upregulation of DNA dependent protein kinase Ku70 and Ku80 is significantly affected by increased expression of Sp1 in small bowel cancer. It was also found that Sp1 could upregulate the expression of insulin-like growth factor binding protein and promote the proliferation of MCF-7 cells (18,19). In prostate cancer DU145 and PC3cell lines, Sp1 knockdown results in a high residual glucose level and a low lactic acid level, suggesting that Sp1 could promote cell metabolism in prostate cancer (20). Liu *et al* (21) found that decreased expression of Sp1 in prostate cell carcinoma reduces cell proliferation, which indicates that Sp1 plays an important role in the development of prostate cancer. Beaver *et al* (22) found that the knockdown of Sp1 in mouse embryos, delays the development, causes mutations and may even result in the death of the embryo. Subsequent studies have found that Sp1 plays a key role in the development of the mouse nervous system and male germ cells (23,24). In the present study, a meta-analysis and a bioinformatics analysis was performed to provide evidence for clarifying the relationship between Sp1 expression and clinicopathological factors in gastric cancer.

Materials and methods

Published study search and selection criteria. Articles included in the analysis were searched for on PubMed and China Academic Journal on 8th June 2018 using the key words: Sp1 AND (gastric OR stomach) AND (cancer OR carcinoma OR tumor OR adenocarcinoma). The inclusion criteria for studies included: i) Published Chinese and English literature limited to patients with gastric cancer; ii) the expression of Sp1 detected through immunohistochemistry in patients with gastric cancer and iii) all patients with gastric cancer did not receive radiotherapy or chemotherapy before surgery. The exclusion criteria included: i) Abstracts, case reports, reviews and meeting notes; ii) studies with a small sample size (n<50); iii) repeat publications or repeat data.

Data extraction and quality assessment. As shown in Table I, the information from all eligible publications was extracted by two reviewers, and included the authors, year of publication, patient country, antibody company, number of cases and controls, risks for cancer, and follow-up outcome. The qualities of the studies were independently assessed by the reviewers according to the Newcastle-Ottawa Scale (NOS; http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm). The method consists of sample selection, comparability and ascertainment of outcome as the number of samples, comparability and results will affect the accuracy of the statistical results. Data was extracted from the Kaplan-Meier survival curves using Engauge Digitizer software (version 4.1; markummitchell.github.io/engauge-digitizer) and then their hazard ratios (HR) and corresponding 95% CI were calculated. No disagreements on the studies to be included were found to exist between the two reviewers. Publication bias was evaluated using a funnel plot. Begg's and Egger's tests were used to assess funnel plot asymmetry.

Bioinformatics analysis. Sp1 gene expression level was analyzed using Oncomine (www.oncomine.org), the largest oncogene chip database and integrated data mining platform. There are two analysis methods. Multiple analysis (fold change), where the expression ratio of each gene under two conditions was calculated, generally in the range of 0.5-2.0, and there was no significant differential expression of the gene. T test (P-value), where the gene whose T statistic exceeds a specific value is detected as an abnormality. Whether the analysis is statistically significant by calculating the confidence of the difference. The differences in Sp1 mRNA level were compared between 80 gastric cancer tissues and 80 normal tissues. All data were log-transformed, median centered for each array, and standard deviation was normalized to a single value for each array. Finally, the Kaplan-Meier plots were used to analyze the prognostic significance of Sp1 mRNA expression. The expression level of Sp1 was divided into high expression group and low expression group according to the best cut off value provided on the Kaplan-Meier plotter.

Statistics analysis. Revman (version 5.3; www.cochrane.es/Download/Files/revman.htm) was used for data analysis. Odds ratios and 95% CI were used to estimate the expression of Sp1 based on the clinicopathological parameters of patients with gastric cancer. First, the heterogeneity of the original documents obtained from PubMed and CNKI was determined. If heterogeneity was not significant, the fixed effect model (Mantel-Haenszel method) was applied. If not, the random effect model (Der Simonian and Laird method) was applied. Heterogeneity effect was quantified using the I^2 test. According to the cutoff values, heterogeneity was subdivided into low, moderate and high degrees of heterogeneity according to the cut-off values of 25, 50 and 75%, respectively. Publication bias was evaluated using funnel plot and quantified using Begg's test and Egger's test to assess funnel plot asymmetry. Meta-analyses were performed with Revman software 5.3 was analyzed using SPSS software (version 10.0; SPSS, Inc.) and the Student's t-test. Two-sided $P<0.05$ was considered to indicate a statistically significant difference.

Results

Literature search results. As shown in Fig. 1, duplicate studies, those that had included animal experiments and reviews were excluded by reading the abstracts. A total of 135 articles were initially retrieved, but only 13 articles were found to investigate the relationship between Sp1 expression and clinicopathological or prognostic indicators of gastric cancer. The exclusion criteria were as follows: i) Studies for which only the abstract available and review and conference proceedings; ii) duplicated studies; iii) studies containing western blot, RT-qPCR, cDNA microarray, or transcriptomic sequencing for maspin expression; and iv) insufficient data (Fig. 1).

Basic characteristics of included articles. There were 13 articles on the relationship between Sp1 expression and

Table I. Characteristics and quality score of the studies.

Author, year	Country	Ethnicity	Antibody supplier	Cases	Ctr	Risk of cancer	Follow-up outcome	Quality	(Refs.)
Jiang *et al*, 2015	China	Asian	Santa Cruz Biotechnology, Inc.	227	-	-	Negative	8	(34)
Jiang *et al*, 2009	China	Asian	Santa Cruz Biotechnology, Inc.	78	20	Increased	-	8	(33)
Zhu *et al*, 2015	China	Asian	Santa Cruz Biotechnology, Inc.	95	20	Increased	-	7	(32)
A *et al*, 2014	China	Asian	Cusabio Technology LLC	66	66	Increased	-	8	(31)
Cui *et al*, 2014	China	Asian	Santa Cruz Biotechnology, Inc.	105	-	-	-	8	(35)
Zhang *et al*, 2011	China	Asian	Bioss, Inc.	76	30	Increased	-	8	(30)
Zhang *et al*, 2014	China	Asian	Shanghai Long Island Biotec. Co., Ltd.	39	39	Increased	-	8	(29)
Zhang *et al*, 2015	China	Asian	Santa Cruz Biotechnology, Inc.	64	40	Increased	Negative	8	(28)
Hua *et al*, 2013	China	Asian	Santa Cruz Biotechnology, Inc.	75	14	Increased	-	8	(27)
Wang *et al*, 2003	China	Asian	Santa Cruz Biotechnology, Inc.	86	57	Increased	Negative	8	(26)
Yao *et al*, 2004	USA	America	Santa Cruz Biotechnology, Inc.	86	-	-	-	8	(12)
Wei *et al*, 2009	China	Asian	Santa Cruz Biotechnology, Inc.	68	-	-	Negative	8	(25)
Hun *et al*, 2013	Japan	Asian	Santa Cruz Biotechnology, Inc.	268	-	-	-	8	(36)

Ctr, control; -, data not provided.

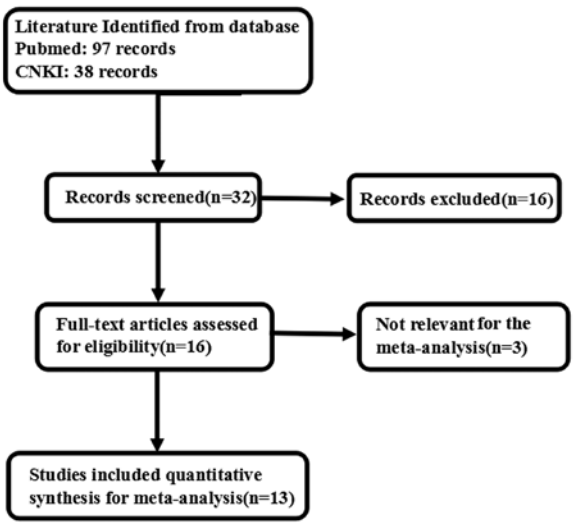

Figure 1. Flow diagram of article selection.

clinicopathological characteristics of gastric cancer (12,25-36). There were 8 articles that included results of normal gastric tissue (26-33). Finally, there were 4 articles that discussed the prognostic significance of Sp1 expression and its relationship with gastric cancer (25-27,34).

Forest plot of odds ratio (OR) for the association between Sp1 expression and clinicopathological parameters of gastric cancer. A total of 8 articles included data on 580 patients with gastric cancer and 286 healthy controls. The overall results showed that the expression of Sp1 was upregulated in gastric cancer and dysplasia (Fig. 2A and B), compared with that of normal mucosa tissue. Forest plots of OR for the association of Sp1 expression were divided based on sex (Fig. 2C), depth of invasion (Fig. 2D), lymph node metastasis (Fig. 2E), TNM staging (Fig. 2F) and Lauren's classification (Fig. 2G). The pathological data available in each article varied. Articles were excluded if a particular clinicopathological characteristic was missing. Therefore, the number of articles in the forest map differed to the initial number of articles. The survival data are showed in Fig. 2H, and based on the 4 aforementioned datasets. The relationship between Sp1 expression and decreased survival rate in gastric cancer patients was investigated and found to be significant (HR, 0.32; 95% CI, 0.22-0.46; P<0.0001).

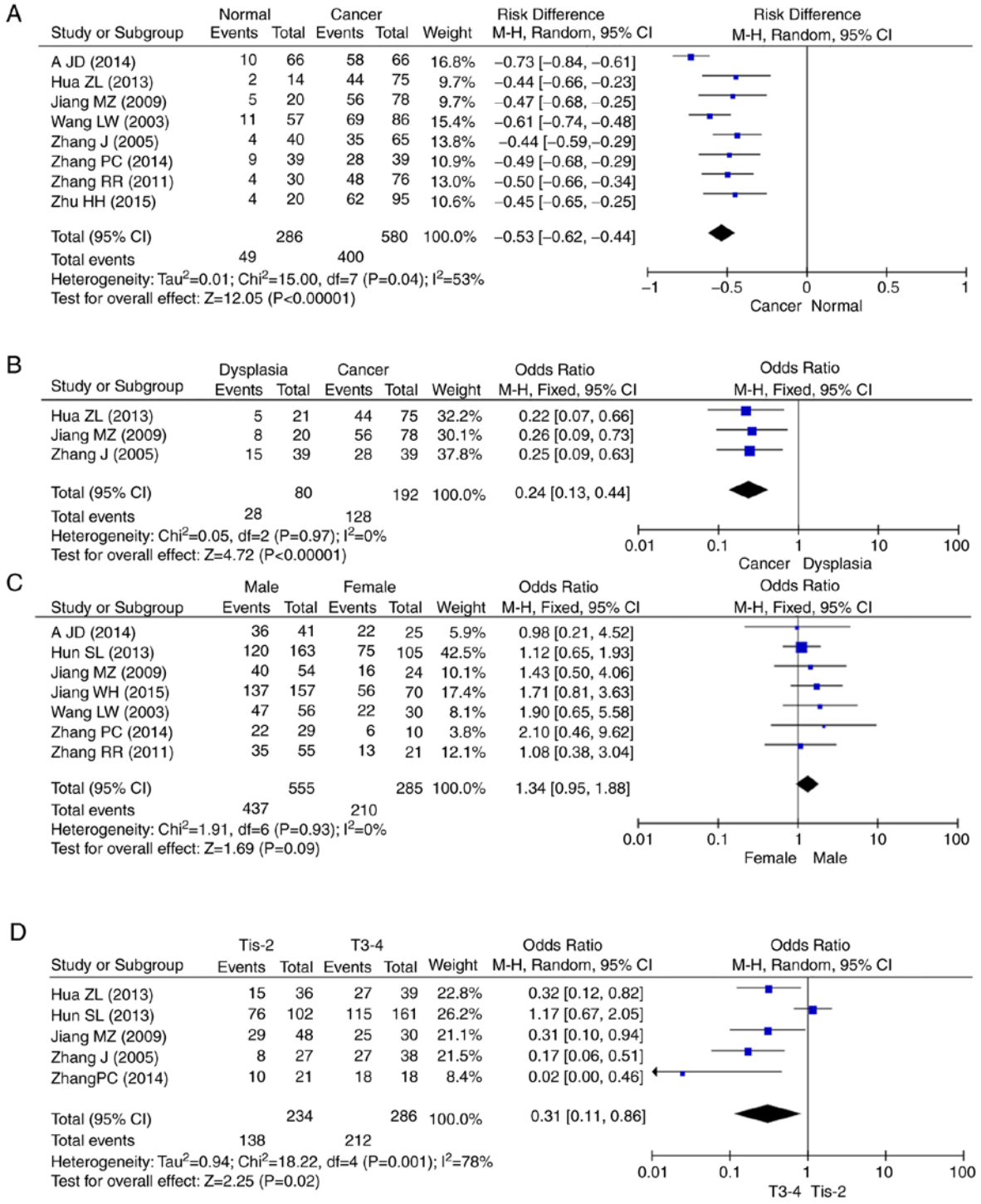

Figure 2. Forest plots of the relationship between Sp1 expression and clinicopathological parameters of gastric cancer. (A) Cancer and normal mucosa. (B) Cancer and dysplasia. (C) Sex (male and female). (D) Depth of invasion (tumor *in situ*-T2 and T3-T4).

Publication bias. Publication bias can be quantitatively determined using funnel diagrams, as shown in Fig. 3. Individual studies were removed from the pooled analysis, and then used sensitivity analysis to assess the impact of the individual study on aggregated results. According to Egger's test, this meta-analysis had no apparent publication bias.

The relationship between Sp1 expression and bioinformatics features of gastric cancer. Cui's and D'Errico's datasets showed that Sp1 mRNA expression was higher in gastric cancer tissue compared with that in normal tissues based on bioinformatics features (Fig. 4A, P<0.05), even when stratified as diffuse, intestinal and mixed-type carcinoma (Fig. 4B-D, P<0.05). According to Kaplan-Meier plots (Fig. 4E and F; Table II), higher Sp1 mRNA expression was negatively associated with the overall and progression-free survival rates of all patients with gastric cancer. In addition, in patients who received surgery alone or 5-FU-based chemotherapy, those with T2, N0, N1-3, N1 and N2, M0, intestinal-type moderately-differentiated, or

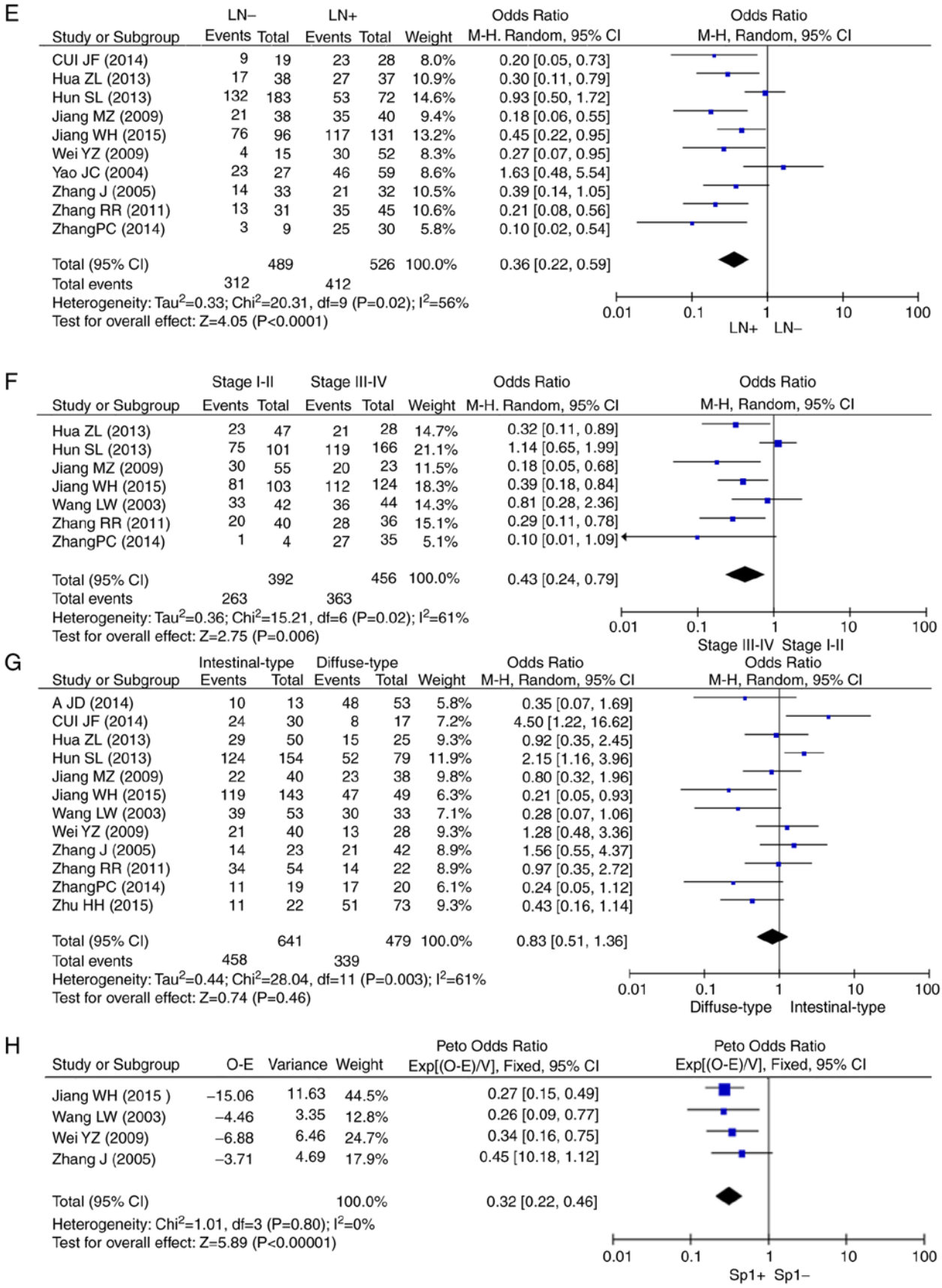

Figure 2. Continued. (E) Lymph node metastasis [LN and (LN- and LN+)]. (F) TNM staging (I-II and III-IV). (G) Differentiation (intestinal-type and diffuse-type). (H) Survival rate (Sp1+ and Sp1-).

Her2-carcinoma were also significantly associated with overall and progression-free survival (P<0.05). Males and T3 patients with gastric cancer with high Sp1 expression showed shorter overall survival times compared with those

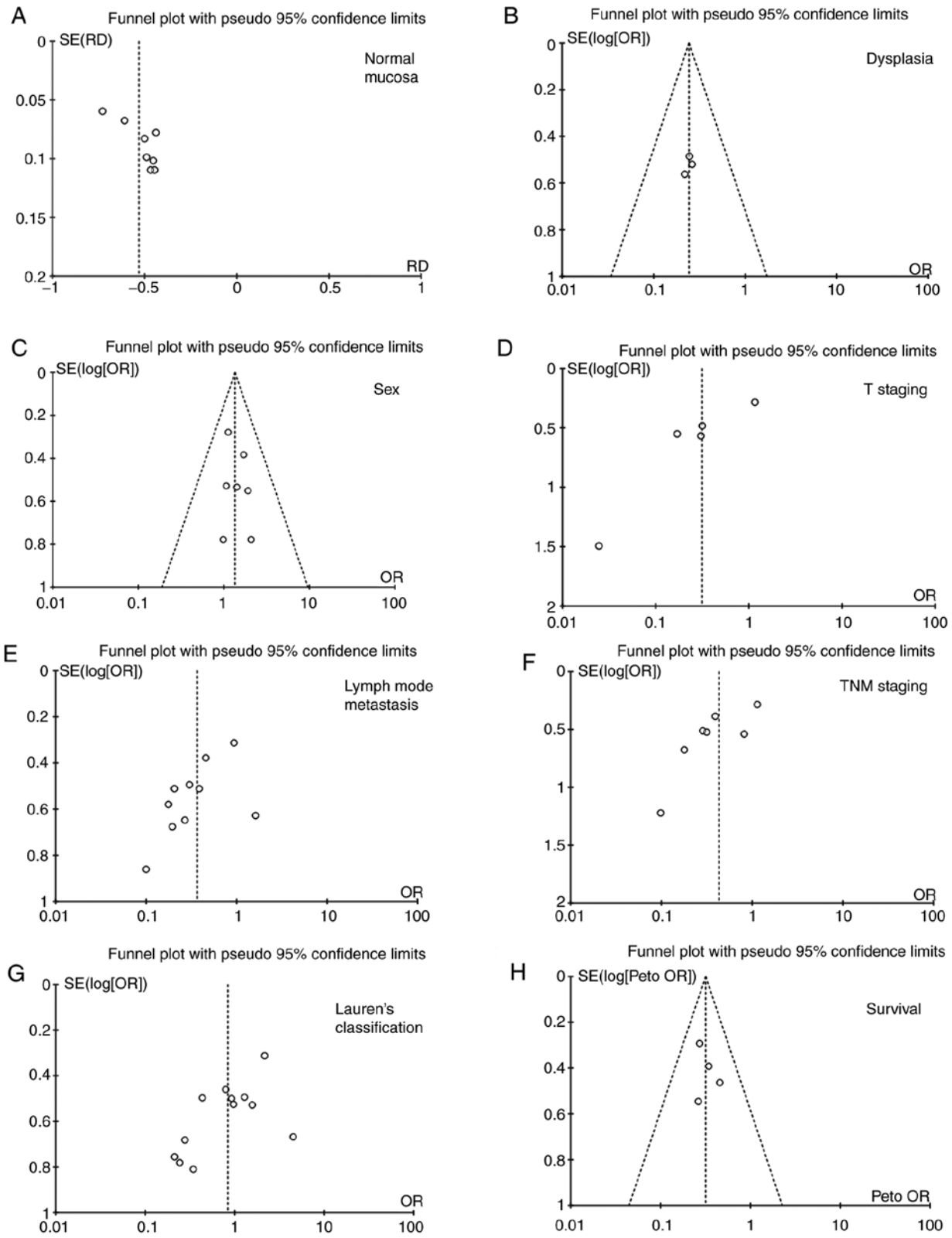

Figure 3. Funnel plot testing publication bias between Sp1 expression and gastric carcinogenesis. Publication bias was analyzed based on risk degrees of Sp1 expression in (A) gastric mucosa and (B) dysplasia for gastric carcinogenesis. Additionally, publication bias was also tested between Sp1 expression and clinicopathological features of gastric cancer, including (C) sex, (D) depth of invasion, (E) lymph node metastasis, (F) TNM stage, (G) differentiation and (H) prognosis. SE, standard error; RD, risk difference.

with low expression (P<0.05), while only it is significantly associated with overall survival (P<0.05). A similar result was obtained for the progression-free survival rates in patients with T4 cancer (P<0.05).

Discussion

Sp1 has a group of zinc-finger proteins that are important transcriptional components in eukaryotic cells, ranging from yeast

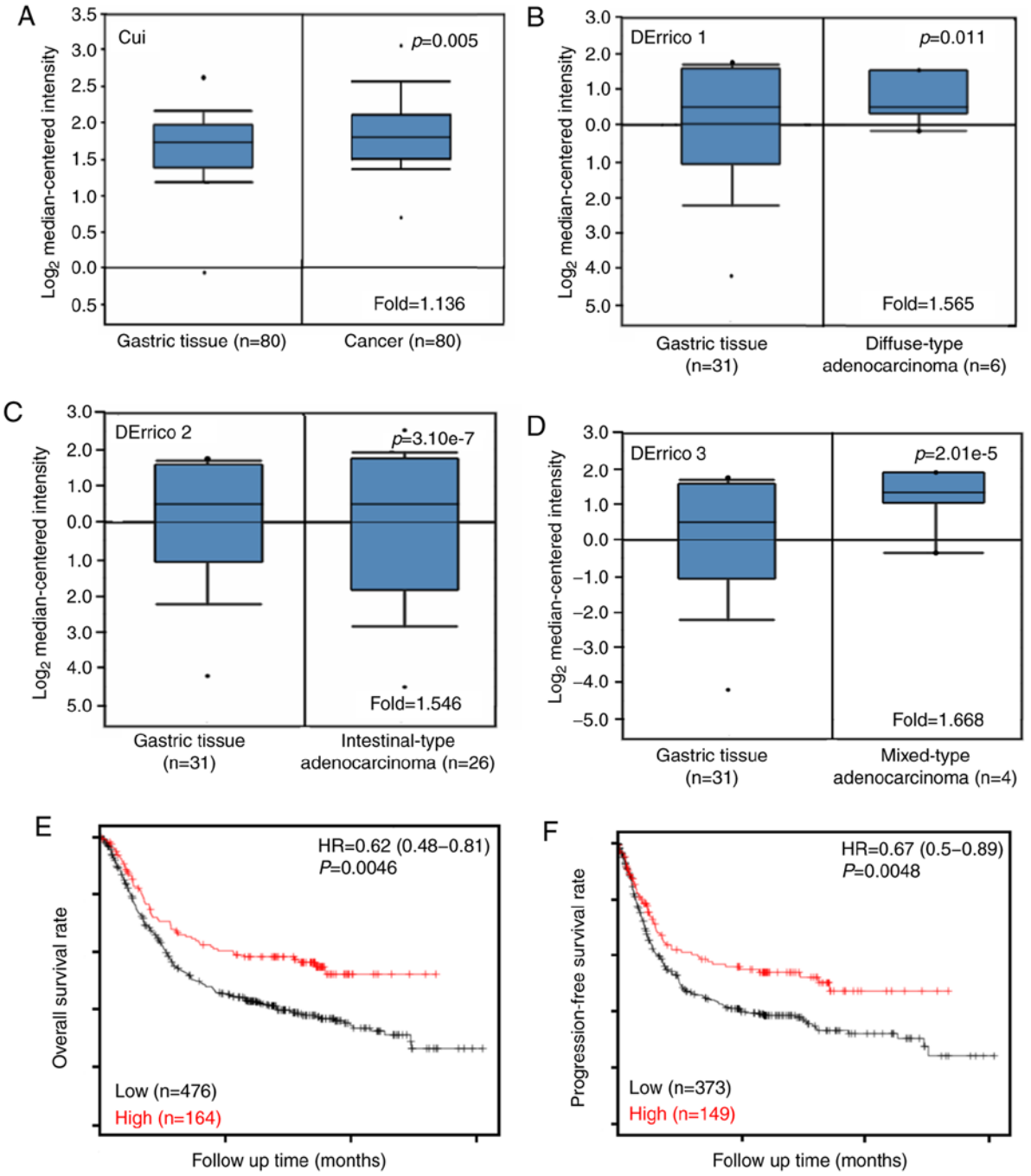

Figure 4. Sp1 mRNA expression in gastric carcinogenesis. Cui's and D'Errico's datasets were employed for the bioinformatics analysis to analyze Sp1 mRNA expression during gastric carcinogenesis. The expression of Sp1 was found to be higher in (A) gastric cancer tissue compared with that in normal gastric mucosa and when stratified as (B) diffuse, (C) intestinal, and (D) mixed-type carcinomas using Lauren's classification. According to data from the Kaplan-Meier plots, Sp1 mRNA expression is negatively associated to (E) overall and (F) progression-free survival rates of patients with gastric cancer. HR, hazard ratio.

cells to vertebrate cells (37). It was found to be overexpressed in gastric cancer and associated with a poor outcome (38). Peng *et al* (39) found that there is a Sp1 binding site in the promoter region of the dickkopf WNT signaling pathway inhibitor 1 (DKK1) gene and that Sp1 overexpression could increase the activity of the DKK1 promoter. Transcriptional enhancer activator domain 1 was able to increase the expression of Sp1 by binding to its promoter in colorectal cancer cells (40). Shi *et al* (41) found that hepatitis B X-interacting protein may activate the fibroblast growth factor 4 promoter via Sp1, which then promotes the migration of breast cancer cells. The transcription activity of Sp1 is enhanced through direct phosphorylation of threonine by p42/p44 mitogen-activated protein kinase (42,43). Jiang *et al* (34) reported that the co-expression of erb-b2 receptor tyrosine kinase 2 and Sp1 are independent prognostic factors of patients with gastric cancer. In order to demonstrate the association with Sp1 expression and its clinicopathological significance, 13 studies were analyzed that met specific inclusion criteria and were moderated to ensure high quality according to NOS scores.

Previous studies show that abnormal Sp1 activation may improve the growth, metastasis and dedifferentiation of

Table II. Prognostic significance of Sp1 mRNA in gastric cancer.

	Overall survival		Progression-free survival	
Clinicopathological features	Hazard ratio	P-value	Hazard ratio	P-value
Sex				
Female	0.66 (0.39-1.11)	0.11	0.66 (0.40-1.09)	0.10
Male	0.63 (0.44-0.89)	0.01	0.57 (0.21-1.51)	0.25
TNM staging				
1	0.19 (0.06-0.57)	<0.01	0.17 (0.06-0.53)	<0.01
2	0.57 (0.26-1.24)	0.15	0.47 (0.21-1.06)	0.06
3	0.60 (0.37-0.97)	0.04	0.66 (0.39-1.12)	0.12
4	0.73 (0.43-1.25)	0.25	0.74 (0.50-1.08)	0.12
T				
2	0.52 (0.37-0.87)	0.01	0.61 (0.38-1.00)	0.05
3	1.29 (0.87-1.89)	0.20	1.31 (0.90-1.91)	0.16
4	0.49 (0.20-1.20)	0.11	0.44 (0.19-1.01)	0.05
N				
0	0.40 (0.16-0.97)	0.04	0.39 (0.16-0.94)	0.03
1-3	0.62 (0.45-0.85)	<0.01	0.65 (0.48-0.88)	<0.01
1	0.57 (0.35-0.94)	0.02	0.56 (0.34-0.92)	0.02
2	0.54 (0.30-0.97)	0.04	0.56 (0.32-1.00)	0.05
3	1.60 (0.84-3.04)	0.15	0.70 (0.40-1.22)	0.21
M				
0	0.61 (0.43-0.85)	<0.01	0.64 (0.46-0.88)	<0.01
1	0.61 (0.32-1.20)	0.15	0.62 (0.34-1.11)	0.11
Perforation complications				
-	1.27 (0.85-1.90)	0.25	0.79 (0.53-1.18)	0.25
Treatment				
Surgery alone	0.67 (0.48-0.94)	0.02	0.69 (0.49-0.97)	0.033
5-fluorouracil-based adjuvant	4.36 (1.64-11.6)	<0.01	3.22 (1.25-8.24)	0.01
Other adjuvant	1.58 (0.63-3.96)	0.3	0.66 (0.28-1.54)	0.34
Differentiation				
Moderately-differentiated	0.48 (0.24-0.94)	0.03	0.45 (0.24-0.87)	0.02
Poorly-differentiated	1.63 (0.98-2.70)	0.06	1.54 (0.95-2.50)	0.08
Lauren's classification				
Intestinal-type	0.50 (0.33-0.77)	<0.01	0.52 (0.36-0.74)	<0.01
Diffuse-type	1.43 (0.99-2.06)	0.05	1.36 (0.94-1.96)	0.10
Mixed-type	2.62 (0.57-12.02)	0.20	2.14 (0.59-7.83)	0.24
Her2 positivity				
-	0.62 (0.47-0.81)	<0.01	0.69 (0.49-0.98)	0.04
+	0.65 (0.41-1.02)	0.06	0.60 (0.37-0.98)	0.04

pancreatic and breast cancers (44-48). In the present study, the expression of Sp1 at mRNA and protein level to be upregulated in gastric cancer tissue, compared with that of normal gastric mucosa, suggesting that Sp1 expression contributes to gastric carcinogenesis. Sp1 expression was also found to be positively associated with depth of invasion, lymph node metastasis and TNM stage of gastric cancer, and the same was true for Sp1 mRNA expression, which indicates that aberrant Sp1 expression can be employed to indicate the pathological behavior of gastric cancers. This result shows that Sp1 mRNA gene expression levels may be used to predict corresponding protein levels.

Reportedly, Sp1 expression is positively related to the poor prognosis of patients with ovarian serous adenocarcinoma and colorectal cancer (49,50). Sp1 upreguation has also been shown to indicate a worse prognosis of breast cancer and hepatocellular carcinoma, as an independent factor (51,52). Chen *et al* (53) reported that the overall prognosis of patients with gastric cancer with high Sp1 levels is significantly poorer compared with that of those with low Sp1 levels. Our

meta-analysis shows that Sp1 overexpression is associated with poor prognosis of human gastric carcinoma. Additionally, the results show that Sp1 mRNA expression is also positively associated with overall and progress-free survival rates of patients with gastric cancer.

Some limitations that exist in our meta-analysis. First, potential publication bias stems from the fact that published results were predominantly positive. Second, the patients included in the studies were only from Asia and America. Different levels of medical development in different areas may also influence the results as different experimental methods may have been used to detect Sp1 expression. Third, survival data were extracted from survival curves, which may affect the results. Fourth, small sample size may influence associations in some articles.

In conclusion, Sp1 protein expression is upregulated in gastric carcinogenesis. Sp1 is positively associated with the depth of invasion and TNM stage of gastric cancer. Sp1 protein expression can be employed as a good potential marker for the prognosis of patients with gastric cancer.

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Availability data and materials

The datasets generated and/or analyzed during the current study are available in the Oncomine database (www.oncomine.org) and Kaplan-Meier plotter (kmplot.com).

Authors' contributions

SS and ZGZ extracted all the relevant information from the eligible publications, independently assessed the quality of the studies and wrote the manuscript. Both authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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